REMARKS

Claims 8-25 are pending and under consideration in this application. All the pending claims currently stand rejected.

In addition to the amendments recited below, claims 11 and 19 have been amended in the present response by replacing the term "r>L+1" with "r≥L+1." These amendments are supported by the specification, e.g., in the example shown in page 23, lines 4-9. In this example, L is set at 4. Hence, L + 1 = 4 + 1 = 5 and the whole nucleotide sequence of the 635-base mRNA is examined for the complementarity between a specific region of 4 or more bases and another site apart by 5 or more bases from said specific region. This means "r" is 5 or more. Therefore, the following relationship can be deduced: r≥L+1.

No new matter has been added by the amendments made herein. Following entry of the instant amendments, claims 8-25 will be pending and under consideration in this application.

35 U.S.C. § 112, first paragraph, rejections

(a) Claims 11-17, and 19-25 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The applicant respectfully traverses the rejection.

From the comments of page 2, line 8, through page 3, line 21, of the Office Action, the applicant understands the Examiner's position to be that there is no clear support for the term "r" being equated to "one plus the number of nucleic bases between the first target region and a complementary region as defined in claims 11 and 19," and that the terminology, within the specification, used to define the value of "r" is "inconsistent with the terminology recited in the claims." The applicant respectfully disagrees with the Examiner's position and offers the following comments to show that there is support for the term "r" being one plus the number of nucleotides between the two complementary sequence regions that form the duplex.

Possibly due to imperfect translation from the original Japanese to English, the applicant concedes that the value of "r" as recited on page 21, lines 6-8, of the instant specification, is not as clear as it could be. In this definition, "r" is indicated to be the distance between the nearest

sites in the complementary, duplexed sequences. Nevertheless, the applicant points out that the definition does not equate this distance with the number of bases between substantially complementary chains and is consistent with the distance being this number of bases plus one, as specified by claims 11 and 19.

The applicant respectfully draws the Examiner's attention to a numerical example, on page 13, lines 5-14 of the instant specification, where a calculation of the ability of a given sequence under consideration to form a substantially double stranded region is given in terms of "r". In this example, "r" is calculated as the numerical position of the first nucleotide of the second sequence in the duplex (43) minus the numerical position of the last nucleotide of the first sequence involved in the duplex (4). The value obtained by this subtraction (43-4 or 39) is the same as one plus the number of bases (38) between the first sequence and the second sequence involved in the duplex. Thus, this numerical example makes it quite clear what is meant by the "distance between the substantially complementary chains" in the definition of "r" on page 21, i.e., it is the number of bases between the substantially complementary chains plus one. The applicant respectfully points out that a written description rejection must be based on what the entire specification discloses, not only on what one or more selected parts disclose.

In light of these considerations, the applicant submits that the definition of "r" as specified in claims 11 and 19 is fully supported by the instant specification and claims 11 and 19 meet the written description requirement.

(b) Claims 8-25 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The applicant respectfully traverses the rejection.

On page 6, lines 7-19, the Examiner states that,

> In practicing the claimed invention, the skilled practitioner would be required to assign the same numerical values to every nucleotide within all selected pairs of complementary sequences. In so doing, all selected pairs of complementary sequences would be indistinguishable on the basis of a summation of the numerical values assigned to the nucleotides contained therein. In this event, the skilled practitioner would first turn to the instant description for guidance in using the claimed invention. However, the description lacks clear evidence how such indistinguishable sequences could be further differentiated so as to select one or

> more regions that have a low summed value relative to another. Therefore, the skilled practitioner would turn to the prior art for such guidance, however the prior art does not discuss how to further differentiate such antisense oligonucleotide sequences. Finally, said practitioner would turn to trial and error experimentation to determine a relationship between said sequences. Such amounts to undue experimentation.

The applicant respectfully disagrees with the Examiner's position, and provides the following comments to show that once an mRNA sequence is analyzed fully, as specified by the instant claims, the same numerical values are not assigned "to every nucleotide within all selected pairs of complementary sequences" and therefore, that the individual nucleotides of a given sequence would be entirely distinguishable from each other in terms of the numerical values computed for and assigned to them.

The instant invention is directed to a method of identifying antisense targets in a given mRNA, or its precursor, by determining which sequences are more likely to form intra-molecular double strand regions (duplexes) and which sequences are less likely to form double strand regions.

This method includes examining the complementarity of a given sequence in the mRNA to other sequence regions in that mRNA, assigning a numerical value to the two regions under consideration based on their probability of forming a complementary duplex, and then repeating this method for each and every other sequence in the mRNA. A relatively high score indicates a higher probability of forming a duplex than would a lower scored sequence.

The calculation for the ability of a given set of two sequences to form a substantially complementary double-strand chain involves the following equation: $((L+1)/r)^F * \exp(|\Delta G|/RT)$, based on L (minimum number of bases in a loop, ≥ 3), r (is the distance between one of the strands and the other strand involved in the duplex (number of bases in a loop +1)), F (an evaluation index for distance r), R (the ideal gas constant) and T (absolute temperature). For a numerical example, see page 13.

The resulting numerical value (for example, 10) of this calculation is assigned to each base in the duplex which was used to calculate the value. Thus, the non-X bases of the hypothetical mRNA sequence: **AUGC**-X-X-X-X-X-X-GCAU, forming the potential duplex,

UACG-X-X-X

: : : : |

AUGC—XXX, would each be assigned the same numerical value from the above calculation (e.g., each nucleotide would be assigned a value of "10").

However, the instant method calls for continued pairing and calculation for the "**AUGC**" sequence with the next potential region of complementarity in the mRNA or its precursor. Following that calculation, the second numerical value is assigned to each nucleotide in the second potential duplex, and then added to the previous values. For example, consider an extended hypothetical sequence from above, AUGC-X-X-X-X-X-X-GCAU-Y-Y-Y-Y-Y-Y-GCAA, where AUGC are at positions 1-4, GCAU at positions 11-14, GCAA are at nucleotide positions 21-24, and the 2-4 and 21-23 sequences form the potential second duplex:

A

ACG ----YYYYYY-UA

: : : |

UGC----XXXXXX--GC

A.

The numerical value resulting from the calculation for the **UGC**/ACG duplex, using the above formula (for example, a value of 8), would be assigned to each nucleotide in the 2-4 and 21-23 duplex. However, since **UGC** have a previous value of 10 already, their new assigned value would be 18, and the 5' **A** would still retain a value of 10. In this way, through repeated comparison, calculation, and numerical assignment, the values of each nucleotide in a given mRNA sequence are differentiated from one another.

Following the final iteration, after each sequence in the mRNA has been compared to every other possible complementary region, each nucleotide and sequence will have a unique assigned numerical value representing the sum of its potential in pairing with the other sequences. Thus, unless all the nucleotides in a given duplex were assigned the same score for each analysis in which they were involved, it is highly unlikely that all the nucleotides in a given duplex, and certainly not all nucleotides in the mRNA as a whole, would have the same

numerical value. Each nucleotide, and more importantly, each potential sequence of nucleotides, would have a distinguishable numerical value to describe how likely it is to form double stranded regions. In view of these above factors, the applicant respectfully submits that one of ordinary skill in the art could readily distinguish between sequences and would not need to resort to trial and error experimentation in order to practice the claimed invention.

In light of these considerations, the applicant respectfully requests that the Examiner withdraw the rejections under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 112, second paragraph, rejections

(a) Claims 8-25 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

On page 7, lines 8-14, of the Office Action, the Examiner states, "claim 8 recites the limitation of 'selecting all pairs of sequences on the target mRNA or its precursor...without independently selecting pairs that are shorter than the selected sequences.' This limitation appears to contradict itself, as it is unclear how a pair of selected complimentary sequence from within a target mRNA or its precursor could ever be 'shorter than the selected sequences.' Applicants are requested to clarify the metes and bounds of this limitation. Claims 9-17 are also included under this rejection due to their dependence from claim 8." The applicant respectfully disagrees and offers the following remarks and amendment to address the Examiner's concerns.

The manner by which two sequences are selected for complementarity analysis is described on page 6, lines 7-19, of the instant specification. In selecting pairs of sequences in the first step of instant claim 8 or 18, the longest sequence (i.e., the region of maximum complementarity) is selected. For example, the applicant asks the Examiner to consider again the hypothetical sequence from above: AUGC-X-X-X-X-X-X-GCAU. When evaluating the potential complementarity of sequence 1-4 with sequence 11-14, if the nucleotides at positions 5 and 10 are not complementary, then the longest possible region of sequence (i.e., 1-4 and 11-14) is considered. In this case, though the sub-sequences "AUG" and "CAU," within this grouping,

are also complementary, this pair would not be independently selected because the sequences are both included in the initial "AUGC-GCAU" duplexed sequences and shorter than the initial duplexed sequences. In an attempt to further clarify this issue, step (a) of instant claim 8 has been amended by the addition of "of sequences" and "and composed of contiguous nucleotides of" to read, "selecting all pairs of sequences on the target mRNA, or its precursor, complementary to each other and separated by at least three nucleotides, but without independently selecting pairs of sequences which are shorter than, and composed of nucleotides of, the selected sequences." This amendment is fully supported by the specification (e.g., page 6, lines 7-23).

The applicant respectfully submits that in view of the above considerations and amendments, the rejection is moot.

(b) Independent claims 8 and 18, and dependent claims 9-17 and 19-25 respectively, stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

From the comments on page 7, line 19, through, page 8, line 8, the applicant understands the Examiner's position to be that claims 8 and 18 recite limitations of assigning the numerical value obtained in step (b) or (g) respectively, to each nucleotide of the paired sequences, where in fact multiple values have been assigned in the previous claims. Thus, it is allegedly unclear which numerical values the steps refer to.

To provide more clarity, the applicant has amended the language of step (c) of claims 8 to read, "assigning the numerical values obtained in step (b) to each nucleotide of each of the paired sequences;" and the language of step (h) of claim 18 to read, "assigning the numerical values obtained in step (g) to each nucleotide of each of the sequences." These amendments render the rejections to claims 8 and 18 (and claims 9-17 and 19-25 dependent on them) moot.

(c) Claims 8-17 stand rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting

to a gap between the necessary structural connections. The applicant respectfully traverses the rejection.

From the comments on page 8, line 12, through page 9, line 5, the applicant understands the Examiner's position to be that the relationship between the "region" or "regions" recited in steps (e) and (f) of claim 8 and steps (l) and (m) of claim 18, respectively, with the sequences of steps (a) and steps (a) and (b) of claims 8 and 18, respectively, are unclear.

The applicant respectfully disagrees with Examiner's position.

The "region" or "regions" as recited in steps (e) and (f) of claim 8 and in steps (l) and (m) of claim 18 are not the sequence(s) recited in step (a) of claim 8 and steps (a) and (b) of claim 18, respectively. The sequences of step (a) of claim 8 are sequences used in the instant methods to calculate the ability of a given nucleotide or region of nucleotides to form a duplex within the greater mRNA structure. In contrast, the "region" or "regions" as referred to in claim (e) and (f) of claim 8, refer to the regions selected from data obtained by this calculation for their relatively low probability of forming a duplex with another region of the mRNA or its precursor. Similarly, the regions of steps (l) and (m) of claim 18 are selected from data calculated from the numerical values assigned to the "regions" of steps (a) and (b). Steps (e) and (f) of claim 8 and steps (l) and (m) of claim 18 have been amended for greater clarity.

The applicant respectfully submits that, in view of the above considerations and amendments, the rejection is moot.

(d) Claim 10 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

On page 9, lines 10-15, of the Office Action, the Examiner states that "Claim 10 recites method steps indexed by the letters (a)-(h). Confusingly, claim 8, from which claim 10 depends, also recites method steps indexed by the same letters (a)-(f). As such, it is unclear which steps (either from claim 8 or claim 10) are properly being referred to in lines 1, 10, 11, 14, 15, and 17 of claim 10." The applicant respectfully submits that from the language of claim 10 set forth in lines 1, 10, 11, 14, 15, and 17, it is clear which steps are being referred to. However, to expedite

prosecution of this application, the applicant has amended claim 10 to recite method steps consecutively indexed using the letters (g)-(n). The rejection of claim 10 is rendered moot by these amendments.

In light of the above considerations and amendments, the applicant respectfully requests that the Examiner withdraw the rejections under 35 U.S.C. § 112, second paragraph.

CONCLUSION

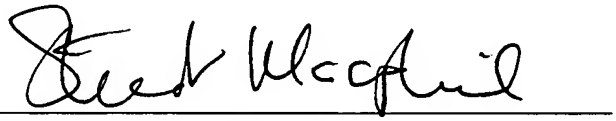
In summary, for the reasons set forth above, the applicant maintains that the pending claims patentably define the invention. The applicant requests that the Examiner reconsider the rejections as set forth in the Office Action, and permit the pending claims to pass to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, the applicant's undersigned representative can be reached at the telephone number listed above.

The applicant submits herewith a request for an automatic extension of time and a check in payment of the extension of time. Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 13797-002002.

Respectfully submitted,

Date: 4/20/06



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